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Total Number of Pages in This Submission	6

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Filing Date	Issued: February 20, 2007
First Named Inventor	James W. Halbrook
Art Unit	1624
Examiner Name	B. Kifle
Attorney Docket Number	N0260.70067US01

ENCLOSURES (*Check all that apply*)

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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 7,179,912

APPLICATION NO. : 09/941,897

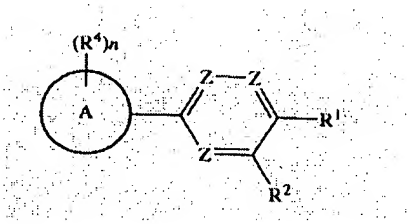
ISSUE DATE : February 20, 2007

INVENTOR(S) : James W. Halbrook et al.

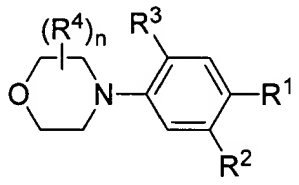
It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Assignee: should be changed from "**ICOS Corporation, Bothell, WA (US)**" to
-- **Luitpold Pharmaceuticals, Inc., One Luitpold Drive, Shirley, NY (US)** --

Claims
In Claim 1, lines 25-30, delete the formula:



and replace with



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APR 16 2007

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(12) **United States Patent**
Halbrook et al.

(10) **Patent No.: US 7,179,912 B2**
(45) **Date of Patent: Feb. 20, 2007**

(54) **MATERIALS AND METHODS TO POTENTIATE CANCER TREATMENT**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/941,897**

(22) Filed: **Aug. 28, 2001**

(65) **Prior Publication Data**

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Related U.S. Application Data

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(51) **Int. Cl.**
C07D 265/30 (2006.01)
C07D 295/02 (2006.01)

(52) **U.S. Cl.** **544/106**; 544/178

(58) **Field of Classification Search** 544/175, 544/106, 178
See application file for complete search history.

(56) **References Cited**

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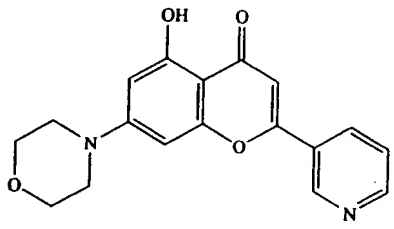
Primary Examiner—Bruck Kifle
(74) *Attorney, Agent, or Firm*—Wolf, Greenfield & Sacks, P.C.

(57) **ABSTRACT**

Compounds that inhibit DNA-dependent protein kinase, compositions comprising the compounds, methods to inhibit the DNA-PK biological activity, methods to sensitize cells the agents that cause DNA lesions, and methods to potentiate cancer treatment are disclosed.

7 Claims, No Drawings

to room temperature, water (about 2 mL) was added, and the mixture was allowed to stir for about 10 min. The contents were transferred to a separatory funnel containing water (5 mL) and extracted with EtOAc (3×15 mL). The organic layer was dried ($MgSO_4$) and concentrated. The concentrate was purified via Biotage chromatography with gradient elution from 100% hexanes to 100% EtOAc to yield 14 mg (12%) of 5-hydroxy-7-morpholin-4-yl-2-pyridin-3-yl-chromen-4-one. Rf=0.22 (100% EtOAc).



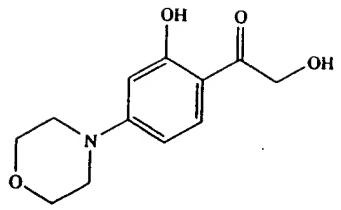
^{1}H NMR ($CDCl_3$, 400 MHz) δ 12.44 (s, 1H), 9.12 (s, 1H), 8.76 (d, 1H), 8.13 (d, 1H), 7.47 (m, 1H), 6.64 (s, 1H), 6.39 (d, 1H), 6.30 (s, 1H), 3.86 (m, 4H), 3.36 (m, 4H). LRMS (Electrospray, positive): Da/e 325.6 (m+1).

EXAMPLE 149

2-Hydroxy-1-(2-hydroxy-4-morpholin-4-yl-phenyl)-ethanone

1-(2-Hydroxy-4-morpholin-4-yl-phenyl)-ethanone was dissolved in triethylamine (12 mL), and trimethylsilyl chloride (1.60 mL, 12.6 mmol) was added dropwise while maintaining the temperature of the solution below 35° C. A solution of sodium iodide (0.54 g, 3.62 mmol) dissolved in acetonitrile (30 mL) was added dropwise without allowing the temperature to rise above 35° C. The reaction was stirred at 22° C. for 16 hours, then poured into ice water/hexanes. The layers were separated and the aqueous layer was washed with hexanes (2×). The combined organics were dried over K_2CO_3 and concentrated in vacuo. This material, 4-(3-trimethylsilanyloxy-4-(1-trimethylsilanyloxy-vinyl)-phenyl]-morpholine, (^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42 (d, 1H), 6.53–6.49 (m, 1H), 6.33–6.31 (d, 1H), 5.06 (s, 1H), 4.53 (s, 1H), 3.87–3.83 (m, 4H), 3.16–3.11 (m, 4H), 0.28 (s, 9H), 0.23 (s, 9H)), was used in the reaction below.

3-Chloroperoxybenzoic acid (1.48 g, 6.0 mmol) was slurried in hexanes (40 mL) and cooled to −78° C. A solution of 4-(3-trimethylsilanyloxy-4-(1-trimethylsilanyloxy-vinyl)-phenyl]-morpholine (1.10 g, 3.01 mmol) dissolved in hexanes (5 mL) was added slowly. The resulting suspension was maintained at −78° C. for 60 minutes then slowly warmed to 22° C. After stirring at 22° C. for 16 hours, the reaction mixture was diluted with methanol and concentrated in vacuo. The residue was redissolved in methanol and concentrated two additional times. The solids were resuspended in EtOAc and washed 2 times with saturated $NaHCO_3$, and once with saturated NaCl then dried over Na_2SO_4. After concentration, the residue was chromatographed on SiO2 using 2:1 hexane/EtOAc then 1:1 hexane/EtOAc. After concentration, the alcohol was recrystallized from EtOAc. (19% yield).

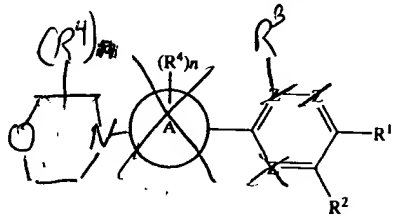


^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.86 (s, 1H), 7.38 (m, 1H), 6.40 (m, 1H), 6.31 (s, 1H), 4.76 (d, 1H), 3.86–3.80 (m, 4H), 3.38–3.32 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): d 199.1, 164.5, 157.0, 130.0, 108.7, 106.1, 100.3, 66.5, 63.7, 47.0. LRMS (Electrospray, negative): Da/e 236.4 (m−1).

Obviously, many modifications and variations of the invention as hereinbefore set forth can be made without departing from the spirit and scope thereof, and, therefore, only such limitations should be imposed as are indicated by the appended claims.

What is claimed is:

1. A compound having a formula



or a pharmaceutically acceptable salt thereof, wherein:

n is an integer 0 through 2;

R^1 is selected from the group consisting of carboxy, cyano, thiocarboxamide, $R^aC(=O)$—;

R^2 is OH; or

R^1 and R^2 are taken together with the carbon atoms to which each is attached to form a monocyclic 5- or 6-membered partially saturated ring, wherein 1, 2, or 3 carbon atoms of R^1 and R^2 optionally are a heteroatom selected from the group consisting of O, N, S, and P, said ring optionally substituted with one or more =O, =S, =NH, OR^h, $N(R^h)_2$, aryl, substituted aryl, heteroaryl, or substituted heteroaryl, said nitrogen or phosphorus heteroatom optionally substituted with a group consisting of aryl, substituted aryl, alkyl, alkyl substituted with $R^aC(=O)$, and R^aC (=O)

R^3, independently, is selected from the group consisting of hydrogen, sulfonamido, sulfamyl, sulfonyl chloride, and sulfo;

wherein R^a is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, heteroaryl, substituted heteroaryl, heterocycloalkyl, and substituted heterocycloalkyl;

wherein R^h, independently, is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl; and

R^4, independently, is selected from the group consisting of OR^h, alkyl, substituted alkyl, aryl, and substituted aryl;

and wherein cycloalkyl is a nonaromatic cyclic hydrocarbon group having three to six carbon atoms;

heterocycloalkyl is a monocyclic, bicyclic, or tricyclic nonaromatic partially unsaturated or saturated ring sys-